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# Silent Warning: The FDA's Ban on Off-Label Speech: Is it Protecting our Safety?

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# SILENT WARNING: THE FDA'S BAN ON OFF-LABEL SPEECH: IS IT PROTECTING OUR SAFETY?

*The FDA's regulation of off-label uses for drugs has been a hotly contested issue. While the FDA seeks to ensure compliance with the regulatory process, drug manufacturers argue that off-label prescribing is a well-regarded practice by physicians and that the regulations and the regulations are impermissible under the First Amendment. Recent cases court cases have ended without a clear resolution as to the First Amendment implications, but message from the FDA remains clear—any kind of advertising of an off-label use may be prosecuted.*

*This paper proposes a compromise between the two extreme positions. Allowable speech and conduct related to off-label prescribing would depend on a number of factors, but the safety of the American public in the face of two distinct dangers would be key amongst these factors. By regulating only advertising which is likely to mislead the public, the regulations can achieve the FDA's goals and meet the requirements of the First Amendment.*

## I. INTRODUCTION

In addition to relying on their training, doctors often use information from drug manufacturers to supplement their knowledge or to inform them of the risks associated with prescription drug use. Such information, however, does not include an expansive class of drug uses; in fact, it cannot. The Food and Drug Administration (FDA), the governmental agency charged with evaluating the safety of food and drugs, limits the type of information manufacturers can give doctors for prescription drug[1] uses that have not been specifically approved.[2] While this may seem like a common-sense approach, the reality is that prescribing drugs for uses that have not been specifically approved, known as "off-label" uses, is a well-regarded and common medical practice.[3]

Recently, Allergan, Inc., the manufacturer of Botox®, filed suit against the FDA, challenging the speech restrictions on off-label drug promotion as violating its First Amendment rights.[4] In addition to its approval for the temporary treatment of wrinkles,[5] Botox® is currently

1. It should be noted at the outset, that this paper concerns prescription drugs, and not over-the-counter (OTC) drugs. OTC drugs have been deemed safe enough to use without medical supervision, while prescription durgs have not. *See* 21 U.S.C. § 353(b) (2006).

2. *See* discussion *infra* Part II.

3. *See infra* Part II.A.

4. Complaint at 26–36, Allergan, Inc. v. United States, No. 09-187 (D.D.C. Oct. 1, 2009).

5. *See* Medication Guide: Botox®, 2010, http://www.fda.gov/downloads/Drugs/DrugSafety/UCM176360.pdf.

approved by the FDA to treat a variety of medical conditions.[6] Although it is not approved to treat all types of spasticity, Botox® is frequently used to treat spasticity in other areas of the body in the same manner that it is used to treat neck spasms.[7] The off-label uses of Botox®, similar to the approved uses, are associated with serious side effects, especially when administered improperly.[8] Allergan distributes safety information on all of its drugs, including information that could inform physicians as to how they could reduce the risk of serious side effects or other negative reactions that can occur from the treatment of spasticity with Botox®.[9] Allergan is prohibited, however, from sending this information to physicians under the regulations surrounding off-label use.[10] Ultimately, Allergan agreed to pay a $600 million penalty and drop the suit against the FDA in exchange for a misdemeanor charge.[11]

With the settlement of the Allergan case and congressional inaction on the subject, the boundary between impermissible regulation and the First Amendment is unclear.[12] This Comment examines the FDA's role in the regulation of off-label drug uses and the First Amendment implications, including whether the drug safety information is commercial speech, and, if so, whether the regulation is permissible as assessed under the test set forth in *Central Hudson Gas & Electric Corp.*

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6. Complaint, *supra* note 4, at 14 (listing Botox®'s approved uses as "strabismus (crossed eyes), blepharospasm (spasm of the eyelids) associated with dystonia, cervical dystonia (involuntary neck muscle contractions), and severe primary axillary hyperhidrosis (excess underarm seating)").

7. *See id.* at 15. Spasticity is a disorder of the central nervous system where certain muscles constantly receive signals to contract. *See* ANNE SHUMWAY-COOK & MARJORIE H. WOOLLACOTT, MOTOR CONTROL: THEORY AND PRACTICAL APPLICATIONS 132–33 (2d ed. 2001). Botox® paralyzes the muscle, preventing it from contracting. *See* Complaint, *supra* note 4, at 14–15.

8. *See* Complaint, *supra* note 4, at 18.

9. *See id.* at 18–20.

10. *See id.* at 24.

11. Catherine Larkin & David Voreacos, *Allergan Will Pay Fine, Plead Guilty to Misdemeanor*, BUSINESSWEEK.COM, Sept. 1, 2010, http://www.businessweek.com/news/2010-09-01/allergan-will-pay-fine-plead-guilty-to-misdemeanor.html; Natasha Singer, *Maker of Botox Settles Inquiry on Off-Label Use*, N.Y. TIMES, Sept. 2, 2010, at A1.

12. Even more specifically, the boundary between permissible regulation and constitutionally protected commercial speech is an area of the law undergoing significant challenge and change. *Compare* Citizens United v. Fed. Election Comm'n, 130 S. Ct. 876, 886 (2010), *and* IMS Health Inc. v. Sorrell, 630 F.3d 263, 266–67 (2d Cir. 2010), *with* IMS Health Inc. v. Mills, 616 F.3d 7, 13 (1st Cir. 2010), *and* IMS Health Inc. v. Ayotte, 550 F.3d 42, 45 (1st Cir. 2008), *cert. denied*, 129 S. Ct. 2864 (2009).

*v. Public Service Commission*.[13] Finally, this Comment proposes a new approach to balance the governmental need for regulating drugs with the speech rights of manufacturers seeking to give important information to physicians. Under this approach, different levels of speech regulation are applied depending on the target audience. This approach recognizes that a regulation may be justified when consumers are the target audience because of the increased safety concerns; however, this government interest does not weigh in favor of regulation for speech directed to physicians.

## II. REGULATION OF SPEECH RELATING TO OFF-LABEL DRUG USE

The FDA has a broad mandate to protect public health by "assuring the safety, efficacy and security" of drugs, biological products, food, and cosmetics.[14] With respect to drugs, the FDA's role is more commonly associated with the drug approval process, but the FDA also has the authority to regulate advertising associated with products that are under its control.[15] The FDA's approval process, when combined with the agency's inability to regulate individual doctors from prescribing off-label, leads to a result where off-label prescribing is a widely accepted and legal practice; however, manufacturers are prohibited from communicating these uses and, in fact, are subject to civil or criminal sanctions.[16]

### *A. Off-Label Prescribing*

FDA regulation of drug advertising, similar to the drug approval process, is based on the drug use, not the composition of the drug. New drugs, or new chemical entities, are subject to a high level of regulation before they can be introduced for sale in the United States.[17] The approval process is time-consuming and expensive.[18] Multiple trials are

13. 447 U.S. 557, 566 (1980).

14. U.S. Food and Drug Administration, About FDA, What We Do, Nov. 18, 2010, http://www.fda.gov/AboutFDA/WhatWeDo/default.htm.

15. *See infra* Part II.A.

16. 21 U.S.C. § 331 prohibits misbranding of a regulated product in interstate commerce. (2006). A drug is misbranded if its labeling includes any information about unapproved uses; labeling is defined expansively to include this form of advertising. *See* discussion *infra* Part II.B.

17. *See* James E. Szalados, *Statutory and Regulatory Controls for Drug Development*, *in* PHARMACEUTICAL LAW: REGULATION OF RESEARCH, DEVELOPMENT, AND MARKETING 1, 24 (Michael E. Clark ed. 2007) [hereinafter PHARMACEUTICAL LAW].

18. *Id.* Timing varies widely for the length of trials. Tarek M. Mahfouz & Janelle S. Crossgrove, *Clinical Trials and the Food and Drug Administration*, *in* CLINICAL TRIALS

required after submission of initial data.[19] New drug entities are first tested on healthy volunteers—that is, volunteers who are unaffected by the condition the drug is intended to mitigate or cure—in trials that can last for about a year.[20] Unlike phase one of the drug trials, phase two requires one hundred to three hundred volunteers who are affected by the condition.[21] These trials evaluate the effectiveness and side effects of the drug and typically take one to two years.[22] Finally, the phase-three trials, which can last from two to ten years, require larger samples to verify the effectiveness and to monitor long-term use.[23] Approval for the drug is specific to the use tested in the clinical trials, not to the chemical composition.

Once prescription drugs are approved and on the market, however, they can be lawfully prescribed for a variety of purposes. Doctors have wide latitude to prescribe drugs; in fact, the FDA has no control over the regulation of doctors, which is a matter for the states.[24]

Off-label prescribing is done for a variety of reasons; in fact, an off-label use may provide the standard of care necessary to treat certain health problems.[25] George Lundberg, M.D., then-editor of the *Journal of the American Medical Association*, testified to Congress that "[p]rescribing FDA-approved drugs for off-label (unlabeled) uses often is necessary for optimal patient care."[26] And regarding these off-label uses he added, "For a product to have the most effective potential benefits, law and regulation should and must follow, not precede, science."[27] Indeed, off-label uses are frequently present on the lists of medically accepted uses for drugs that the government is required to

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HANDBOOK 227, 234–35 (Shayne Cox Gad ed. 2009) ("The various steps a new drug endures from its synthesis to the time it makes it to the market as a drug vary in length . . . [with] an average of 7 years in clinical trials. . . .").

19. Szalados, *supra* note 17, at 62.

20. *Id.* at 64.

21. *Id.*

22. *Id.*

23. *Id.* at 65.

24. *See* Gonzales v. Oregon, 546 U.S. 243, 272 (2006) (noting that states regulate most aspects of the medical profession).

25. *See* Rebecca Dressler & Joel Frader, *Off-Label Prescribing: A Call for Heightened Professional and Government Oversight*, 37 J.L. MED. & ETHICS 476, 476 (2009).

26. *Promotion of Drugs and Medical Devices for Unapproved Uses: Hearing Before the Subcomm. on Human Resources and Intergovernmental Relations of the H. Comm. on Government Operations*, 102d Cong. 100, 103 (1991) (statement of George Lundberg, Editor, *Journal of the American Medical Association*).

27. *Id.*

keep for its reimbursements to Medicare and Medicaid.[28]

Doctors may prescribe a drug off-label based on their knowledge of the drug's mechanism of action[29] or based on a published report in the literature. Moreover, some new treatment methods are discovered incidentally.[30] New uses for drugs are sometimes discovered by observing the treatment of patients who suffer from multiple conditions when doctors notice an alleviation of one condition when treating another.[31] This was the case with Verapamil®, a drug approved for treatment of cardiovascular conditions that is now used to treat headaches. Patients taking Verpamil® for cardiovascular diseases began reporting that they were having fewer headaches while on Verapamil®.[32] Thus, drugs are often used and prescribed legally for uses beyond those approved in the FDA's drug approval process.[33] In fact, approximately one out of every five drugs prescribed is prescribed off-label.[34]

Another prevalent use of off-label drugs is in patients with terminal diseases or diseases that take a significant toll on the patient's quality of life.[35] A recent study has shown that more than half of all cancer patients receive off-label treatments not only because cancer treatment is constantly evolving,[36] but also because patients who are running out of

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28. *See* 42 U.S.C. § 1396r-8(k)(2)–(6) (2006).

29. *See* Daniel B. Klein & Alexander Tabarrok, *Do Off-Label Drug Practices Argue Against FDA Efficacy Requirements? A Critical Analysis of Physician's Argumentation for Initial Efficacy Requirements*, 67 AM. J. ECON. & SOC. 743, 755–56 (2008).

30. *See id.*

31. *Id.* at 756. In response to a question about off-label use, a physician stated:

> Some of the newer antihistamines were initially only indicated for the treatment of seasonal allergic rhinitis, but not for perennial allergic rhinitis. Well, there is no difference in the allergic cascade and mechanism of seasonal and perennial allergic rhinitis and their response to antihistamines. Consequently, most allergists prescribed them for both forms of rhinitis before the FDA published its official approval of indications.

*Id.* at 755.

32. *Id.* at 756.

33. *See* Paul W. Radensky et al., *Potential Liability for Drug Companies, Health Care Providers, and Insurers: Off-Label Prescribing and Internet Advertising*, *in* PHARMACEUTICAL LAW, *supra* note 17, at 239, 254.

34. *See* David C. Radley et al., *Off-Label Prescribing Among Office-Based Physicians*, 166 ARCHIVES INTERNAL MED. 1021, 1023 (2006).

35. *See* Roxanne Nelson, *Should Experimental Cancer Therapies be Available Outside Clinical Trials?*, MEDSCAPE MED. NEWS, June 18, 2009, http://www.medscape.com/view article/704591.

36. *See* National Cancer Institute, Understanding the Approval Process for New Cancer Treatments, Q&A: Off-Label Drugs, Jan. 6, 2004, http://www.cancer.gov/clinicaltrials/

options push for experimental treatments.[37]

In fact, the popularity of off-label uses has only increased in recent decades, perhaps due in part to the rigorous and expensive nature of the approval process. The new drug approval process may cost hundreds of millions of dollars.[38] A discovery of a new use may occur after the drug has exceeded or is near the end of its normal patent protection; thus, the economic incentives for manufacturers to seek approval for new drug uses when a drug has gone off-patent is significantly reduced.[39]

### *B. Regulatory Framework Limiting Speech Related to Off-Label Drug Uses*

The Food, Drug, and Cosmetic Act (FDCA) controls the labeling and promotion of drugs. Indeed, the negative drug labeling restrictions that result in off-label promotion bans are a product of multiple provisions of the FDCA.[40] During the drug approval process, the FDA also evaluates the proposed labeling to determine whether the labeling is "false or misleading"[41] and whether the drug is safe for approval under the proposed labeling.[42] Just as a manufacturer would not be allowed to change the composition of a drug, a manufacturer similarly cannot change the labeling without approval.[43] If a manufacturer changes the labeling such that it "prescribe[s], recommend[s], or suggest[s]" a new use for that drug, then the FDA deems it a new drug.[44] As a result, the manufacturer must apply for approval of the drug for that use,[45] or else

learning/approval-process-for-cancer-drugs/page5. Pediatrics and oncology are but two examples. *See Guidance for Off-Label Use of Drugs*, 7 LANCET NEUROLOGY 285, 285 (2008) (discussing the high prevalence of off-label use in the field of neurology); Randall S. Stafford, *Regulating Off-Label Drug Use—Rethinking the Role of the FDA*, 358 NEW ENGL. J. MED. 1427, 1427 (2008) (noting that antipsychotics have a 60% rate of off-label use).

37. *See* Nelson, *supra* note 35.

38. *See generally* Christopher P. Adams & Van V. Brantner, *Estimating the Cost of New Drug Development: Is It Really $802 Million?*, 25 HEALTH AFF. 420 (2006). Costs can vary widely depending on the type of therapy and the size of the firm. *Id.* at 426–27. In 2006, the expected cost of developing an HIV/AIDS drug was $479 million, while drugs to treat respiratory disorders had an expected cost of $1.13 billion. *Id.* at 426 (statistics featured in exhibit 5). Likewise, for one large pharmaceutical company the expected cost per drug was $521 million, while at another firm it was $2.119 billion. *Id.* at 427.

39. *See* Adams & Brantner, *supra* note 38 and accompanying text.

40. *See* 21 U.S.C. §§ 301, 321, 331, 352, 355 (2006).

41. *See id.* § 355(e).

42. *See* discussion *supra* Part I.

43. *See* 21 U.S.C. § 355(a).

44. *See id.* § 321(p).

45. *See id.* § 355(a).

the manufacturer is treated as if it introduced a new drug into the market without approval.[46]

The FDA's broad control over labeling is part of the reason for its broad authority over manufacturer speech. The FDCA defines the word "label" rather narrowly to suggest some nexus between the printed matter that comprises the label and the product itself.[47] The Act defines "labeling" to include "all labels and other written, printed, or graphic matter (1) upon any article or any of its containers or wrappers, or (2) accompanying such article."[48] In contrast, the regulations define labeling much more expansively to include the following:

> Brochures, booklets, mailing pieces, detailing pieces, file cards, bulletins, calendars, price lists, catalogs, house organs, letters, motion picture films, film strips, lantern slides, sound recordings, exhibits, literature, and reprints and similar pieces of printed, audio, or visual matter descriptive of a drug and references published . . . for use by medical practitioners . . . which are disseminated by or on behalf of its manufacturer.[49]

Thus, the regulations go further than the Act, and prohibit much more than printed material accompanying the drug.

An alternate source of regulation is the FDA's control over "false and misleading" drug labeling.[50] The FDA interprets this authority to prohibit "scientific claims about the safety, effectiveness, contraindications, side effects, and the like regarding prescription drugs."[51] Under this definition, the accuracy of the scientific claim is not at issue; rather, the FDA asserts that these statements are false and misleading because they may lead a person to believe that the statement was validated by the FDA.[52]

Finally, the FDA controls manufacturer speech on off-label uses through its regulation of drug advertisements.[53] Drug advertisements

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46. *See id.* § 331.

47. *See id.* § 321(k) ("The term 'label' means a display of written, printed, or graphic matter upon the *immediate* container.") (emphasis added).

48. *Id.* § 321(m).

49. 21 C.F.R. § 202.1(l)(2) (2010).

50. *See* 21 U.S.C. § 352(a) (2006).

51. Wash. Legal Found. v. Friedman, 13 F. Supp. 2d 51, 67 (D.D.C. 1998) *vacated on other grounds sub. nom*, Wash. Legal Found. v. Henney, 202 F.3d 331 (D.C. Cir. 2000).

52. *See, e.g.*, *id.*

53. 21 U.S.C. § 352(n) (2006).

include advertising directed at both consumers and physicians. Although the Act permits drug advertisements that meet certain standards,[54] the regulations make clear that an advertisement for a prescription drug "shall not recommend or suggest any use that is not in the labeling accepted in such approved new-drug application."[55]

The penalties for off-label marketing can be severe. In addition to criminal and civil fines, the House of Representatives recently passed a bill that allows the Department of Health and Human Services (HHS) to exclude a drug manufacturer's products from coverage by government payers such as Medicare and Medicaid if the drug maker is guilty of a felony or a misdemeanor.[56] Recently, Pfizer paid the largest fine in history—$2.3 billion—for promoting the drug Bextra® for the treatment of pain beyond its approved use for the treatment of menstrual pain.[57]

These restrictions present a difficult but important question: what, if any, First Amendment rights do manufacturers have to give information about their product? While there is a strong case for government regulation of misleading or false speech—indeed, it has been upheld by the courts[58]—when the speech in question is truthful, or a scientific fact, can governmental regulation still pass First Amendment scrutiny?

## III. LITIGATION CONCERNING OFF-LABEL PRESCRIBING AND ITS LIMITATIONS

The litigation surrounding the First Amendment and the scope of the FDA's regulatory authority provides some indication of how courts may assess this issue going forward. Unfortunately, litigation addressing the specific issue of FDA regulation of off-label promotion has been addressed only in cases that were vacated on other grounds.

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54. *See id.*

55. 21 C.F.R. § 202.1(e)(4) (2010).

56. 42 U.S.C. § 1320a-7(a)(3) (2006).

57. *See* Gardiner Harris, *Pfizer to Pay $2.3 Billion to Settle Inquiry Over Marketing*, N.Y. TIMES, Sept. 3, 2009, at B4. The $2.3 billion figure represents the combined criminal and civil fines. *Id.* The criminal fine alone was $1.3 billion. *Id.* There was evidence that Pfizer's off-label promotion was misleading. *See id.* Manufacturers who promote their drugs with truthful and non-misleading statements are subject to similar penalties. *See, e.g.*, Complaint, *supra* note 4, at 6–14.

58. Efforts to prohibit deceptive drug advertising have been present since the first Food and Drug Act was enacted in 1906. *See, e.g.*, Seven Cases of Eckman's Alternative v. United States, 239 U.S. 510, 517 (1916); United States v. Johnson, 221 U.S. 488, 498 (1911).

### *A.* Washington Legal Foundation

Prior to the Food and Drug Administration Modernization Act (FDAMA), the FDA sought to respond to manufacturers' previous attempts to inform physicians about the off-label uses of their drugs. The FDA issued guidances that limited the distribution of journal articles and textbooks about off-label uses as "improper labeling and/or promotion."[59] The Washington Legal Foundation (WLF), a non-profit public interest and policy center, challenged these policies as violating the First Amendment rights of its members to receive information concerning off-label uses.[60] Judge Lamberth of the United States Court of Appeals for the District of Columbia found that these restrictions violated the First Amendment and that the FDA could regulate truthful scientific speech only under limited circumstances.[61]

Shortly after this decision, however, Congress passed the FDAMA, which modified many of the previous guidances to allow distribution of materials if the manufacturer complied with several requirements, including providing the FDA with the materials and submitting an application.[62] The FDA appealed the lower court decision but conceded at oral argument that nothing in the FDAMA gave the FDA independent authority to regulate manufacturer speech.[63] Rather, the FDA viewed the guidance as a "safe harbor," which would "ensur[e] that certain forms of conduct would not be used against manufacturers."[64] WLF agreed; and the D.C. court found that there was no longer any controversy, dismissed the appeal, and vacated the lower court's decision.[65]

But the issue was not resolved. In March 2000, the FDA published a notice in the *Federal Register* indicating that it would evaluate a manufacturer's conduct on a case-by-case basis to determine if its distribution of written materials constituted misbranding.[66] WLF filed a motion with the district court to enforce the previous injunction against

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59. *See* Wash. Legal Found. v. Kessler, 880 F. Supp. 26, 28 (D.D.C. 1995).

60. *See id.* at 27–28.

61. *See* Wash. Legal Found. v. Friedman, 13 F. Supp. 2d 51, 74 (D.D.C. 1998).

62. 21 U.S.C. § 360aaa(a)–(b) (2006) (terminated 2006).

63. *See* Wash. Legal Found. v. Henney, 202 F.3d 331, 332, 335 (D.C. Cir. 2000) (noting that "the dispute between the parties has disappeared before our eyes").

64. *Id.* at 335.

65. *Id.* at 336–37.

66. Decision in Washington Legal Foundation v. Henney, 65 Fed. Reg. 14,286 (Mar. 16, 2000).

the statement.[67] Judge Lamberth agreed that the notice was unconstitutional, but ultimately concluded that he could not enforce the injunction because the court of appeals had vacated it.[68] Thus, the *WLF* litigation ended without resolving the dispute.[69]

### *B.* Thompson v. Western States Medical Center

The permissible scope of FDA regulations was determined by the Supreme Court in a closely related area: drug compounding.[70] In *Thompson v. Western States Medical Center*, licensed pharmacists challenged a provision in the FDAMA that restricted advertising of compounded drugs.[71] Drug compounding is a process by which a pharmacist or doctor combines drug ingredients to prepare medications that are not commercially available or to tailor a drug to an individual's specific need.[72] The practice is similar to off-label prescribing because compounding results in an unapproved drug use, although all the ingredients have been approved, individually, at some point by the FDA.[73] The FDAMA's advertising restriction was enacted in response to the FDA's concerns that pharmacists were manufacturing and selling drugs in a compounded form to avoid the approval process.[74] The Court struck down FDA efforts to regulate advertising by pharmacists,[75] in part because the FDA had non-speech related means of preventing large-scale drug compounding.[76]

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67. *Henney*, 128 F. Supp. 2d at 13.

68. *See id.* at 15.

69. For a more detailed explanation of the *WLF* litigation, see generally Richard M. Cooper, *The WLF Case Thus Far: Not with a Bang, But a Whimper*, 55 FOOD & DRUG L.J. 477 (2000).

70. *See* Thompson v. W. States Med. Ctr., 535 U.S. 357, 360 (2002).

71. *Id.*

72. *Id.* at 360–61. For example, a pharmacist may compound drugs when a patient has an allergy to an approved medication. *Id.* at 361. Additionally, allergies to typical carriers for the active ingredient of a medicine can be compounded in a different carrier. State boards of pharmacy regulate the individual pharmacists and locations. *See* International Academy of Compounding Pharmacists, Frequently Asked Questions, http://www.iacprx.org/site/PageServer?pagename=FAQs (last visited May 14, 2011).

73. *See* International Academy of Compounding Pharmacists, *supra* note 72.

74. *W. States*, 535 U.S. at 362.

75. *Id.* at 377. In *Western States*, neither party challenged the commercial aspect of the speech at issue. *Id.* at 366. The Court analyzed the speech in question under the *Central Hudson* test. *Id.* at 367–68.

76. *Id.* at 372.

### *C. Litigation's Limitations*

*Western States* illustrates a victory for compounding pharmacists in a situation very similar to that of off-label drug prescribing. The success of *Western States*, in contrast to the *WLF* litigation, illustrates one of the difficulties of judicially resolving this issue. The cases directly on point to the FDA speech restrictions on off-label prescribing are either (1) interest group litigation, like the WLF cases, or (2) criminal or civil charges relating to bad actors.[77] While the WLF has had some successes, interest group litigation in general suffers from the lack of a concrete dispute and is at the whim of the party on the opposite side of the fight. While the WLF was successful at the district court level, the FDA was able to moot the issue by withdrawing the contested position (and later reasserting it).[78] Currently, interest group litigation is at a standstill because the ambiguous Bush-era regulations allowing some non-promotional reprint distribution have never been formally repealed. The reprint guidance seemingly has little weight, or there is very little that the FDA considers non-promotional. A formal repeal might result in more interest group litigation on the subject.

The other area where litigation typically arises is in the criminal context after a manufacturer is charged with violating the regulations.[79] In contrast with the compounding pharmacists who initiated a suit on their own accord, the FDA is able to pick its battles in the off-label context by bringing charges against the most egregious offenders. Although the compounding pharmacists did not have to argue against assertions that their conduct was poorly intentioned, off-label litigants are often surrounded by facts that make the First Amendment a poor defense.[80]

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77. *See, e.g.*, United States v. Caputo, 288 F. Supp. 2d 912, 914 (N.D. Ill. 2003); Settlement Agreement at 2–4, United States v. Novartis Pharms. Corp., No. 08-CV-2588 (E.D. Pa), No. 06-CV-1630 (E.D. Pa), No. 04-CV-1664 (E.D. Pa), No. 03-CV-1551-T-30-TGW (M.D. Fla) (referring, in addition, to a criminal case against Novartis); Superseding Misdemeanor Information at 3–5, United States v. Gleason, No. 06-CR-229 (E.D.N.Y. Aug. 8, 2008); Press Release, U.S. Dep't of Justice, Biopharmaceutical Firm Intermune to Pay U.S. Over $36 Million for Illegal Promotion and Marketing of Drug Actimmune (Oct. 26, 2006), http://www.justice.gov/opa/pr/2006/October/06_civ_728.html; Press Release, U.S. Dep't of Justice, Eli Lilly and Company to Pay U.S. $36 Million Relating to Off-Label Promotion (Dec. 21, 2005), http://www.justice.gov/opa/pr/2005/December/05_civ_685.html; Press Release, U.S. Dep't of Justice, Serono to Pay $704 Million for the Illegal Marketing of AIDS Drug (Oct. 17, 2005), http://www.justice.gov/opa/pr/2005/October/05_civ_545.html.

78. Wash. Legal Found. v. Henney, 202 F.3d 331, 332 (D.C. Cir. 2000).

79. *See* sources cited *supra* note 77.

80. *See* Larkin and Voreacos, *supra* note 11 (discussing whistleblower allegations that Allergan participated in illegal kickback schemes).

## IV. FIRST AMENDMENT APPLICATION TO PROMOTIONAL RESTRICTIONS

Determining whether the regulations that prevent manufacturers from communicating off-label uses are contrary to the requirements of the First Amendment requires a preliminary analysis of commercial and noncommercial speech. Although manufacturers have a profit motive as to any potential sale, the question is more complicated when the speech at issue is scientific fact used for the purposes of promotion. For speech that is noncommercial, the government has a higher burden to prove that the regulation is constitutional.[81] Commercial speech, however, receives less protection than noncommercial speech and is typically analyzed under the *Central Hudson* test.[82]

### *A. What is Commercial Speech?*

The text and the history of the First Amendment provide little guidance about the meaning or breadth of the Free Speech Clause. The First Amendment to the United States Constitution simply states, "Congress shall make no law respecting an establishment of religion, or prohibiting the free exercise thereof; or abridging the freedom of speech, or of the press; of the right of the people peaceably to assemble, and to petition to the Government for a redress of grievances."[83]

Over time and following the ratification of the Fourteenth Amendment and the incorporation of the Bill of Rights, the Supreme Court's view on the guarantees of speech has expanded, but the reach of the First Amendment is still being defined by the Court.[84] In the context of content-based regulations, some categories of speech receive less protection than others: categories of speech that receive the least protection are fighting words,[85] obscenity,[86] libel,[87] and speech inciting violence.[88] These categories of speech fall outside of the protection of the First Amendment because they have little value to society and are outweighed by society's interest in order and morality.[89]

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81. *See* Cent. Hudson Gas & Elec. Corp. v. Pub. Serv. Comm'n, 447 U.S. 557, 563 (1980).
82. *See* Thompson v. W. States Med. Ctr., 535 U.S. 357, 367 (2002).
83. U.S. CONST. amend. I.
84. *See, e.g.*, Citizens United v. Fed. Election Comm'n, 130 S. Ct. 876, 886 (2010).
85. *See* Chaplinsky v. New Hampshire, 315 U.S. 568, 572 (1942).
86. *See* Miller v. California, 413 U.S. 15, 23–24 (1973).
87. *See* Gertz v. Robert Welch, Inc., 418 U.S. 323, 342–43 (1974).
88. *See* Brandenburg v. Ohio, 395 U.S. 444, 447 (1969).
89. *Chaplinsky*, 315 U.S. at 572.

### *B.* Valentine v. Chrestensen

While the Constitution makes no mention of a distinction between commercial and noncommercial speech, the Supreme Court articulated the distinction in *Valentine v. Chrestensen*[90] In that case, Chrestensen was a businessman who advertised tours of his submarine through the distribution of a handbill.[91] However, a city sanitary code prohibited the distribution of commercial and business advertising materials.[92] Undeterred by the sanitary code, Chrestensen printed two-sided handbills: one side was an advertisement for the tour, and the other was a protest against the City Dock Department's refusal to let him moor the submarine at the dock of his choice.[93] In resolving the case against Chrestensen, the Court created the commercial speech doctrine: "We are . . . clear that the Constitution imposes no . . . restraint on government as respects purely commercial advertising."[94] Thus, at the outset, the Court viewed commercial speech as deserving no First Amendment protection.

### *C.* Virginia State Board of Pharmacy v. Virginia Citizens Consumer Council

Since the broad statement that commercial speech is not protected in *Valentine*, "the Court has granted commercial speech some protection, although considerably less than other [types] of speech."[95] In *Virginia State Board of Pharmacy v. Virginia Citizens Consumer Council*, the Court struck down a Virginia law that made advertising prescription drug prices unprofessional conduct for pharmacists licensed in Virginia.[96] The Court found that the law was an impermissible restriction on speech and, although the speech was commercial, it warranted some amount of protection.[97] The Court also noted that "commonsense differences" between commercial speech and noncommercial speech "suggest that a different degree of protection is necessary."[98]

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90. 316 U.S. 52, 54 (1942).
91. *See id.* at 52–53.
92. *Id.* at 53.
93. *Id.*
94. *Id.* at 54 (creating the commercial speech doctrine without citing a single authority).
95. *See* Alex Kozinski & Stuart Banner, *Who's Afraid of Commercial Speech?*, 76 VA. L. REV. 627, 628 (1990).
96. 425 U.S. 748, 770 (1976).
97. *Id.*
98. *Id.* at 771–72 n.24.

Distinguishing between commercial speech and noncommercial speech can be problematic. The different rationales offered in a footnote in *Virginia State Board of Pharmacy* shed light on the Court's idea of the distinction.[99] The first rationale proposed is that the truth of commercial speech is more easily verifiable by its disseminator than by others.[100] The other rationale posited is that because commercial speech is engaged in for profit, it is more durable than noncommercial speech and is less susceptible to being chilled by government regulation.[101] The Supreme Court also has added to the definition of commercial speech in *Pittsburgh Press Co. v. Pittsburgh Commission on Human Relations*.[102] In that case, the Court defined commercial speech as speech that does "no more than propose a commercial transaction."[103] The Supreme Court has also held that speech is not commercial solely because the speaker has a commercial interest.[104]

The Court confronted a similar situation in *Bolger v. Youngs Drug Products Corp.*, where informational pamphlets about contraceptives were at issue.[105] The pamphlets contained information relating to sexually transmitted diseases and family planning but also referred to a particular contraceptive brand.[106] The Court laid out a three-factor test that looked beyond the *Pittsburgh Press* definition of commercial speech to determine whether the speech was motivated by commercial concerns or noncommercial concerns.[107]

*Western States* is also important because, unlike prior Court precedent, it did not place on a premium on the truthfulness of the commercial speech in question.[108] In early cases the Court relied on the rationales for the commercial speech doctrine put forth in *Virginia State Board of Pharmacy* to determine if commercial speech warranted a departure from the strict scrutiny given to other types of speech.[109] Later, in *44 Liquormart, Inc. v. Rhode Island*, the Court struck down a

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99. *See id.*

100. *Id.*

101. *Id.* For a criticism of the rationales given in *Virginia State Board of Pharmacy* see Kozinski & Banner, *supra* note 95, at 634–38.

102. 413 U.S. 376 (1973).

103. *Id.* at 385.

104. *See id.*

105. 463 U.S. 60, 61–62 (1983).

106. *Id.* at 62–63 n.4.

107. *Id.* at 65–68.

108. *See* Thompson v. W. States Med. Ctr., 535 U.S. 357, 367–68 (2002).

109. *See, e.g.*, Metromedia, Inc. v. City of San Diego, 453 U.S. 490, 505 (1981).

Rhode Island law banning the advertisement of liquor prices.[110] The plurality opinion noted that "when a State entirely prohibits the dissemination of truthful, nonmisleading commercial messages for reasons unrelated to the preservation of a fair bargaining process, there is far less reason to depart from the rigorous review that the First Amendment generally demands."[111] The plurality opinion also noted that truthful, nonmisleading commercial speech was not affected by either of the rationales given in *Virginia State Board of Pharmacy* and that such speech "justifies reviewing its complete suppression with added deference."[112] The decision in *44 Liquormart* suggests that truthful commercial speech should be afforded the same level of protection as noncommercial speech.[113] Following *Western States*, however, the truthfulness of commercial speech merely remains one element of the *Central Hudson* test.[114]

### *D. Can Scientific Speech Be Commercial?*

The threshold question of whether truthful and nonmisleading scientific speech is commercial speech has not received much attention.[115] In the *WLF* litigation, WLF argued that the marketing practices at issue were "scientific and academic speech, which is entitled to the highest level of First Amendment protection."[116] The court, however, focused on the commercial aspect of the speech based on the speaker being the manufacturer; yet, the court also recognized it as "the speech of others—the work product of scientists, physicians and other academics."[117] In that case, the court quoted *Bolger*, perhaps to similarly distinguish between the speaker's motivations for the speech.[118] The court held that the manufacturer's speech has a commercial motive, while a scientist, speaking about the same thing, has a noncommercial motive.[119] But can motivation really be determined that simply? For example, scientists could also be driven by a profit motive depending on

110. 517 U.S. 484, 489 (1996).

111. *Id.* at 501.

112. *Id.* at 502.

113. *See id.* at 501. Note, however, that the *44 Liquormart* Court did apply the *Central Hudson* test. *See id.* at 504–08.

114. Thompson v. W. States Med. Ctr., 535 U.S. 357, 367–68 (2002).

115. For instance, this prong was not an issue in *Western States*. *Id.* at 368.

116. Wash. Legal Found. v. Friedman, 13 F. Supp. 2d 51, 59 (D.D.C. 1998).

117. *Id.* at 62.

118. *See id.* at 64.

119. *Id.*

where the funding for research comes from or where they conduct research. Similarly, it is possible that a manufacturer could have a motive unrelated to selling products for scientific speech when the speech is intended to educate or even prevent liability.[120] Of course, manufacturers are primarily sellers of products, and thus, it can be argued that anything they do serves this primary purpose whether it is generally educational or not.

Under the guidance provided in *Pittsburg Press*, commercial speech does "no more than propose a commercial transaction."[121] Joining Allergan, WLF argued in its amicus brief that the speech relating to Allergan's safety information does much more than propose a commercial transaction.[122] Specifically, the WLF argued that Allergan's safety information also had scientific and clinical value.[123] It further argued that "[t]ruthful, accurate, nonmisleading speech that implicates issues of both scientific inquiry and public health is high-value speech," and thus its restrictions "should be subject to strict scrutiny."[124]

Although courts have not yet found FDA regulations on off-label promotion or similar regulations to be noncommercial speech,[125] if a court did find such speech to be noncommercial, it is unlikely that the regulations would be able to meet the higher level of First Amendment protection.[126]

### *E.* Central Hudson*: The Test for Commercial Speech Regulations*

When regulated speech is commercial, courts apply the four-pronged test established in *Central Hudson Gas & Electric Corp. v. Public Service Commission* to determine if the regulation violates the

120. *See* discussion *infra* Part V.

121. Pittsburgh Press Co. v. Pittsburgh Comm'n on Human Relations, 413 U.S. 376, 385 (1973).

122. *See* Brief of the National Spasmodic Torticollis Ass'n, the National Spasmodic Dysphonia Ass'n, Allied Educational Foundation, and Washington Legal Foundation as Amici Curiae in Support of Plaintiff's Motion for Preliminary Injunction at 20, Allergan, Inc. v. United States, No. 09-1879 (D.D.C. Nov. 19, 2009).

123. *Id.*

124. *Id.*

125. *See, e.g.*, Wash. Legal Found. v. Friedman, 13 F. Supp. 2d 51, 64 (D.D.C. 1998).

126. Content-based regulation of noncommercial speech requires that the regulation be *necessary* to meet a *compelling* state interest and that it be narrowly tailored to that interest. *See, e.g.*, Simon & Schuster, Inc. v. Members of N.Y. State Crime Victims Bd., 502 U.S. 105, 118 ("In order to justify such differential treatment, 'the State must show that its regulation is necessary to serve a compelling state interest and is narrowly drawn to achieve that end.'").

First Amendment.[127] The *Central Hudson* test directs the court to determine whether (1) the speech "concern[s] lawful activity" and is not misleading, (2) "the asserted governmental interest is substantial," (3) the "regulation directly advances the governmental interest asserted," and (4) the regulation is "not more excessive than . . . necessary to serve that interest."[128]

1. Prong One: Off-Label Speech Concerns a Lawful Activity and is Truthful and Nonmisleading

The first prong of the *Central Hudson* test asks whether the speech in question concerns a lawful activity and is not false or misleading.[129] The First Amendment does not protect false or misleading commercial speech; but to be considered misleading, the speech must be "inherently misleading," not just "potentially misleading."[130]

Courts have found that off-label speech concerns lawful activity because the conduct underlying the speech—physicians prescribing drugs off-label—is a lawful activity.[131] The FDA has long recognized the practice of off-label use among physicians and has not challenged the lawfulness of physicians prescribing off-label uses.[132]

The FDA has also argued that off-label speech is inherently misleading because the FDA has not evaluated and approved its content,[133] apparently contending that people expect that all food and drug claims have been approved by the FDA; thus, the mere presence of drug claims that are not subject to FDA approval is misleading in itself. The Court has rejected this argument, adding that the argument "exaggerates [the FDA's] overall place in the universe."[134] Therefore, truthful, nonmisleading speech regarding an off-label use satisfies the first prong of the *Central Hudson* test.

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127. *See* 447 U.S. 557, 566 (1980).

128. *Id.*

129. *Id.*

130. *See* Ibanez v. Fla. Dep't of Bus. & Prof'l Regulation, 512 U.S. 136, 145–46 (1994).

131. *See* Wash. Legal Found v. Friedman, 13 F. Supp. 2d 51, 66 (D.D.C. 1998).

132. More importantly, the FDA does not have authority to regulate the practice of medicine; rather, that authority rests with the states. *See* Gonzales v. Oregon, 546 U.S. 243, 272 (2006).

133. *See Friedman*, 13 F. Supp. 2d at 67.

134. *Id.*

2. Prong Two: Is the Integrity of the Regulatory Process a Substantial Governmental Interest?

Even truthful and nonmisleading speech can be regulated when the government can satisfy *Central Hudson*'s final three prongs.[135] To do so, the government must first show that it has a substantial interest for its regulation.[136] Yet, according to some commentators, there can never be a legitimate governmental interest for the suppression of truthful speech.[137]

On occasion, the Court has rejected the proposition that suppression of information could meet this prong.[138] In *Virginia State Board of Pharmacy*, where price advertisements for prescription drugs were at issue, the state argued that the ban on prescription drug prices was necessary, because if advertising was permitted, consumers would shop for the best prices, which would result in a loss of a stable pharmacist-consumer relationship.[139] The Court noted that this rationale represented a "highly paternalistic approach," and the choice "between the dangers of suppressing information, and the dangers of its misuse if it is freely available" had already been made by the First Amendment in favor of the free availability of information.[140]

On the other hand, in *Western States*, the Court concluded that the government's interest in preserving the effectiveness and integrity of the new drug approval process was substantial.[141] Similarly, the FDA has advanced this same interest to justify restrictions on off-label speech in the *WLF* litigation because off-label uses also avoid the new drug approval process.[142] While courts have accepted these propositions to satisfy the second prong of the test, there is some argument that the effectiveness of the drug approval process alone is not substantial enough to justify the regulation of off-label promotion. For example, while the speech at issue in *Western States* was of the type that "does no more than propose a commercial transaction,"[143] speech regarding off-

135. Thompson v. W. States Med. Ctr., 535 U.S. 357, 367 (2002).

136. *Id.*

137. *See* Richard A. Samp, *Courts are Arriving at a Consensus on Food and Drug Administration Speech Regulation*, 58 FOOD & DRUG L.J. 313, 316 (2003).

138. *See id.*

139. Va. State Bd. of Pharmacy v. Va. Citizens Consumer Council, 425 U.S. 748, 768 (1976).

140. *Id.* at 770.

141. Thompson v. W. States Med. Ctr., 535 U.S. 357, 369 (2002).

142. *See* Wash. Legal Found. v. Friedman, 13 F. Supp. 2d 51, 70 (D.D.C. 1998).

143. *W. States*, 535 U.S. at 367 (quoting Edenfield v. Fane, 507 U.S. 761, 767 (1993)).

label uses carries much more social value than a mere price advertisement. The *Allergan* case illustrates that off-label speech can have particularly high value when it concerns safety information.

In the *WLF* litigation, the FDA also argued that there was an additional substantial government interest in safety.[144] The FDA argued that the restrictions served to prevent dangerous uses of drugs[145] and that it was merely following its mandate, noting that "the ordinary citizen . . . has little ability to protect himself or herself from the potential harm associated with unproven uses of drugs and devices."[146] But, as will be discussed below, although safety is an important governmental interest,[147] the regulation does not pass the third prong when the speech actually promotes, and thus does not inhibit, safety.

### 3. Prong Three: The Regulations May Directly Advance the Governmental Interest

The third prong of the *Central Hudson* test requires the government to show that the regulation directly advances its substantial interest.[148] To satisfy this prong, the commercial speech regulation must alleviate the harms the government asserts "to a material degree."[149]

In *Western States*, the Court assumed, but did not decide, that the regulation directly advanced the asserted governmental interest of maintaining the integrity of the new drug approval process.[150] Similarly, in the *WLF* litigation the court found that the restrictions on the dissemination of scientific materials directly advanced the interest of ensuring that manufacturers seek approval for new devices.[151] The court stated that limiting a manufacturer's marketing options is "one of the few mechanisms available to [the] FDA" to compel manufacturers to seek new drug approval for off-label uses.[152] This rationale could be persuasively presented to apply to any future challenges as well.

A related governmental interest that the FDA may face a greater hurdle overcoming is consumer safety. While consumer safety is

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144. *See Friedman*, 13 F. Supp. 2d at 69.

145. *Id.*

146. *Id.* at 57 (internal quote omitted).

147. *See, e.g.*, Posadas de P.R. Assocs. v. Tourism Co., 478 U.S. 328, 341 (1986).

148. *See* Cent. Hudson Gas & Elec. Corp. v. Pub. Serv. Comm'n, 447 U.S. 557, 566 (1980).

149. Edenfield v. Fane, 507 U.S. 761, 770–71 (1993).

150. *See* Thompson v. W. States Med. Ctr., 535 U.S. 357, 371, 378 (2002).

151. Wash. Legal Found. v. Friedman, 13 F. Supp. 2d 51, 72 (D.D.C. 1998).

152. *Id.*

certainly an important interest, whether a regulation which prohibits manufacturer-to-physician speech can directly advance this interest is more problematic. The regulation must alleviate the harms of speech, not regulate speech that could itself alleviate harms. A logical and persuasive argument could be made that a goal of safety—or the goal of preserving the regulatory process as it is ultimately concerned with safety—could never be directly advanced by restricting the dissemination of safety information, when that information is truthful and nonmisleading. This further harkens back to the choice "between the dangers of suppressing information, and the dangers of its misuse if it is freely available."[153] The benefits of the information must outweigh its potential misuse.

4. Prong Four: The Regulations are More Extensive than Necessary to Achieve the Asserted Interest

The fourth prong of the *Central Hudson* test requires that the commercial speech restrictions be narrowly tailored to the government's asserted interest.[154] This prong has been used successfully by parties seeking to challenge FDA policies as too restrictive. For example, in *Western States*, the Court determined that other means besides restricting advertisements on drug compounding could advance the government's interest in protecting the new drug approval process.[155] Likewise, the WLF succeeded on this prong in *Friedman* by showing that restrictions on off-label uses were not narrowly tailored, because they excluded too much information, not just the information related to the government's interest.[156]

While the Court has concluded that the FDA's means of promoting the new drug process are very limited, and that manufacturer restrictions are one of the few tools they have to promote the new drug process,[157] there must be other ways to achieve this goal. Promotion of the new drug process does not require that all manufacturer speech be restricted. In fact, regulations which allow some—but not all—promotion of off-label uses would achieve the same goal in promoting new drug uses.

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153. Va. State Bd. of Pharmacy v. Va. Citizens Consumer Council, 425 U.S. 748, 770 (1976).

154. *See* Cent. Hudson Gas & Elec. Corp. v. Pub. Serv. Comm'n, 447 U.S. 557, 565–66 (1980).

155. *W. States*, 535 U.S. at 372.

156. *See Friedman*, 13 F. Supp. 2d at 73–74.

157. *See id.* at 72.

## V. FAILURE TO WARN

Issues of drug manufacturer speech and the FDA regulations also implicate tort cases.[158] Related to the First Amendment issues, the current restrictions on off-label speech also raise another important issue on which there is no clear consensus: whether a manufacturer can be held liable for failure to warn regarding an off-label use, especially given that they are currently prohibited from doing so. Failure to warn is a products-liability claim that can proceed on a theory of negligence or on a theory of strict liability,[159] but both theories allege that the manufacturer of a product had a duty to warn of the specific risks associated with that product and that the manufacturer's failure to do so caused the plaintiff's injury.[160] One policy rationale for failure to warn is that manufacturers have assumed a special responsibility in selling their products and that if the manufacturer knows of the danger of a particular use, it should be required to give an adequate warning.[161] Manufacturers are not, however, liable for failure to warn about uses that they do not know about and uses that are not foreseeable.[162] State courts have not focused on the fact that the manufacturer's ability to warn about off-label uses is restricted.

Some courts have found manufacturers liable for failure to warn when they had knowledge of the off-label use.[163] In *Anderson v. Sandoz Pharmaceuticals Corp.*, the plaintiff was prescribed the drug Parlodel® to treat her hyperprolactimia.[164] Parlodel® was not approved or recommended for hyperprolactimia; therefore, the prescription for Parlodel® was off-label.[165] The plaintiff alleged that Parlodel® caused her to suffer cardiac arrest, a side effect which the label warned of generally, but not specifically with respect to hyperprolactimia.[166] Denying the drug manufacturer's motion for summary judgment, the court noted that the manufacturer both knew of Parlodel's® off-label use and had commissioned a research study regarding the negative effects of

158. *See id.* at 73 ("[T]o the extent that the tort regime looks to FDA approval as the definition of the 'standard of care,' the call to get new uses on-label will come from sources other than the FDA.").

159. RESTATEMENT (THIRD) OF TORTS: PRODUCTS LIABILITY § 2 cmt. a (1998).

160. *Id.* § 2 cmt. i.

161. *Id.* § 2 cmt. a.

162. *See* RESTATEMENT (SECOND) OF TORTS § 395 (1965).

163. *See* Anderson v. Sandoz Pharms. Corp., 77 F. Supp. 2d 804, 809 (S.D. Tex. 1999).

164. *Id.* at 805.

165. *Id.*

166. *Id.*

Parlodel®.[167] The court determined that the defendant may have "prevented [the patient's physician] from making an informed choice."[168] Other courts have followed this logic with respect to warning about off-label uses, basing liability on the knowledge of the use and the failure to consider the restrictions on off-label use.[169]

Some courts have determined that manufacturers have a duty to warn only about the dangers associated with the normal use of the product.[170] In *Rhoto v. Ribando*, a plaintiff sued both a physician and manufacturers of a drug after the physician prescribed a combination of drugs to help the plaintiff lose weight and she subsequently suffered a stroke.[171] The trial judge directed a verdict for the defendant manufacturers, which was affirmed on appeal.[172] The Louisiana Court of Appeals emphasized that the manufacturers need warn only of the dangers associated with normal use of its products.[173] This reasoning, however, only partially protects manufacturers from being held liable for failing to warn when they are restricted from doing so. In many cases, an off-label use is a normal use of the product and a manufacturer could still be held liable under this rationale.

While this holding is questionable, the fact that advertising off-label uses is restricted creates a conflict: while warnings should be given under state tort law, they should not be given under federal laws and regulations. The holding is further questionable in light of *Wyeth v. Levine*,[174] a recent case where the issue of the preemption of state claims by the FDA reached the highest Court. In *Wyeth v. Levine*, the manufacturer's label on a drug called Phenergan® allowed the drug to be administered by direct injection as a highly potent way of delivering the drug to get prompt effects.[175] The label also warned that if the drug entered an artery, it could cause gangrene; however, it did not tie that risk to direct injection.[176] That label, including the suggested

167. *Id.* at 807–08 n.4, 809.

168. *Id.* at 809.

169. *See, e.g.*, Knowlton v. Deseret Med., Inc., 930 F.2d 116, 119–20, 123 (1st Cir. 1991) (holding that a manufacturer was liable for failure to warn about an off-label use for their device that was approved for venipunctures but was commonly used as atrial lines in open-heart surgery).

170. *See* Rhoto v. Ribando, 504 So. 2d 1119, 1123 (La. Ct. App. 1987).

171. *Id.* at 1120.

172. *Id.* at 1121, 1126.

173. *Id.* at 1123.

174. Wyeth v. Levine, 129 S. Ct. 1187, 1193 (2009).

175. *Id.* at 1191.

176. *Id.* at 1191–92.

administration, was approved by the FDA.[177]

The plaintiff-respondent Diana Levine, who sought treatment of a severe migraine headache and associated nausea and dehydration, was given an intra-muscular injection of Phenergan®, but it did not provide any relief.[178] She returned later in the day and was given a "push injection" of the drug (as opposed to an IV-drip).[179] The drug was incorrectly injected into an artery, causing complications and eventually gangrene.[180] As a result, her forearm was amputated, ending her career as a musician.[181] She reached a $700,000 malpractice settlement with the clinic where the injection was given, and sued Wyeth in state court, arguing that the pharmaceutical firm should have revised its label to bar IV-push injections.[182] Her case went to the Vermont Supreme Court where the court ruled in her favor, holding that Wyeth was obliged to comply with a Vermont common law duty to not use a particular form of risky drug administration.[183]

Wyeth appealed the case to the United States Supreme Court, arguing that the manufacturer should not be liable under state law for a label that the FDA approved.[184] But the Court disagreed in a 6-3 decision, holding that federal approval of labels giving warnings about effects of drugs does not bar lawsuits under state law claiming inadequate warnings of a health risk.[185] This approach was read by many to indicate that the responsibility rests with the manufacturer, and that Wyeth was required to fill out the paperwork to change the label once they had information regardless of the approval process.[186]

Based on the outcome in *Wyeth*, one argument for allowing some level of promotion is because torts—particularly failure to warn, negligence, and fraud—offer better alternatives to incentivize rigorous safety testing by pharmaceutical companies and to provide compensation for those who are injured by unsafe drugs.[187] This

177. *Id.* at 1191–93.
178. *Id.* at 1191.
179. *Id.*
180. *Id.*
181. *Id.*
182. Levine v. Wyeth, 944 A.2d 179, 182–83 (Vt. 2006).
183. *Id.* at 188.
*184. See Wyeth*, 129 S. Ct. at 1191.
185. *Id.*
186. Byron Stier, *Promotion of Off-Label Use: In Favor of a Regulatory Retreat*, 19 ALB. L.J. SCI. & TECH. 609, 616 (2009).
187. *See id.* at 609.

argument not only targets manufacturers who fail to give good information or make safe drugs, but it also provides an incentive for them to do so. Further, this approach provides the most protection for patients, through the threat of massive tort litigation against non-compliant pharmaceutical companies.[188]

## VI. THE FDA SHOULD TAKE A NEW APPROACH TO OFF-LABEL PROMOTION

Currently, with the *Allergan* case settled and ambiguous guidance from the FDA, drug makers are in a state of uncertainty regarding what type of speech is allowed. While there were hopes that higher courts might consider the issue on the facts of *Allergan*, such an opportunity has yet to arise because *Allergan*, like many other cases, ended without a clear resolution. Clarity is greatly needed. In a time when the country is focused on lowering heath care costs, including a greater availability of generic treatments, the motivation is even greater. Moreover, the uncertainty in this area is a potential liability for drug manufacturers who may have the duty to warn in some cases, but who may also be limited in their ability to provide such warnings.

The problem of what can and should be done about this problem has received some attention from scholars and practitioners.[189] The drug approval process itself has been criticized as overly burdensome and as creating a lack of incentive for drug manufacturers to seek approval for uses that have limited commercial reward. Commentators have suggested that Congress could provide incentives for approval of new uses.[190] While congressional incentivizing might solve a piece of the puzzle, the reality is that the drug approval process is slow. Because the drug would already be on the market as approved for other uses, and because the FDA has no power to limit off-label prescribing, there would still be a significant period of time where manufacturers would be both liable for warnings and statutorily prohibited from issuing such guidance.

Opposite of the currently allowable disclosures, some commentators have proposed that the only approach consistent with the First Amendment is to allow all types of manufacturer conduct for promotion

188. *Id.* at 610.

189. For an argument that the FDA's regulations are not problematic under the First Amendment, see generally Jacob Rogers, Essay, *Freedom of Speech and the FDA's Regulation of Off-Label Drug Uses*, 76 GEO. WASH. L. REV. 1429 (2008).

190. *See, e.g.*, Margaret Gilhooley, *Drug Safety and Commercial Speech: Television Advertisements and Reprints on Off-Label Uses*, 47 SAN DIEGO L. REV. 845, 855 (2010).

of off-label uses.[191] However, this approach does not overcome the fact that courts have repeatedly held that the government has a substantial interest in maintaining the integrity of the new drug process.[192] Beyond this problem, though, allowing all off-label use might be going further than necessary to balance the tension between the First Amendment, the drug maker's rights, and the safety interests of consumers. Courts could take a middle road, allowing some, but not all, manufacturer speech or conduct. Allowable speech and conduct would depend on a number of factors, but the safety of the American public in the face of two distinct dangers would be key amongst these factors. The danger associated with allowing unrestricted manufacturer speech related to off-label uses is that some uses may be less safe, and thus some speech could lead to increased unsafe uses. However, because manufacturer speech occurs in different settings and different mediums, the safety implications could differ based on the targeted audience. An approach that considers the method of speech and the audience could separate promotion aimed at physicians from those aimed primarily at consumers. Media outlets are numerous, and it would be impossible to guarantee that there would be no cross contamination; however, if most off-label promotion was limited to media that is directed to doctors, the increased safety risks that could be caused by increased off-label use would be minimized. This approach would also reduce the other safety risks associated with not providing adequate instructions or warnings to doctors because these communications would be allowed.

One piece of media that could be permissibly restricted is broadcast media. Television and radio advertising, even for approved uses of prescription drugs, has met wide-spread criticism because it is seen as interfering with the doctor-patient relationship.[193] Critics point to evidence that doctors are likely to prescribe a drug that they would not have prescribed for a patient with the same condition when a patient requests a drug that the patient has seen advertised,[194] and that doctors

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191. *See* Jeffrey N. Gibbs et al., *Ripe for Revision: Reassessing the Constitutionality of Food and Drug Administration Restrictions on Protected Speech*, 58 FOOD & DRUG L.J. 331, 344 (2003) (arguing that "[n]othing in First Amendment jurisprudence supports the use of peer review as the gatekeeping test . . . to achieve constitutional protection").

192. *See* Thompson v. W. States Med. Ctr., 535 U.S. 357, 369 (2002).

193. *See* Meredith B. Rosenthal et al., *Promotion of Prescription Drugs to Consumers*, 346 NEW ENG. J. MED. 498, 504–05 (2002) (remarking on how "direct-to-consumer" advertising affects the physician-patient relationship).

194. *See* Joel Lexchin & Barbara Mintzes, *Direct-to-Consumer Advertising of Prescription Drugs: The Evidence Says No*, 21 J. PUB. POL'Y & MARKETING 194, 198 (2002); *cf.* John E. Calfee, *Public Policy Issues in Direct-to-Consumer Advertising of Prescription*

who do not prescribe the requested drug must spend the little time they have with patients explaining why they do not wish to prescribe an advertised product.[195] This situation would be compounded if drug manufacturers were able to advertise on television for off-label uses.

On the other hand, scientific journals and instructional guides are examples of media that clearly fall in the category where regulation should be deemed impermissible. Scientific journals, while occasionally falling into the hands of lay people, are written and primarily read by doctors, as would be any leaflet, instructions, or warnings provided directly to doctors' offices. Scientific conferences would also be appropriate places for manufacturers to present research to medical professionals. This approach would have the benefit of encouraging peer review of manufacturer research on drugs, which is further beneficial because manufacturers often have the most information on the uses of the drugs they make.

There is also precedent for the FDA to take this bifurcated approach. Recently, cigarettes and tobacco products came under the FDA's control.[196] Previously, the regulations on cigarette advertising were set by Congress to balance the Free Speech rights of the manufacturers, the interests of public health, and the sales of a dangerous product. In 1970, Congress banned the manufacturers from advertising cigarettes by means of television and radio.[197] The ban on cigarette advertising on television and radio is similar in its policy aims to bans on off-label promotion, and the cigarette advertising ban has the benefit of having been deemed constitutional. In *Capital Broadcasting Co. v. Mitchell*, radio stations acted to enjoin enforcement of the Public Health Cigarette Smoking Act of 1969, which prohibited broadcasting of cigarette advertisements, on First Amendment grounds.[198] The Supreme Court, without issuing an opinion, upheld the statute.[199] While an explicit congressional ban of off-label prescribing would likely be upheld for the same reasons the Court has allowed the bans on cigarette

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*Drug*s, 21 J. PUB. POL'Y & MARKETING 174, 187 (2002) (arguing that the current studies are not conclusive and that direct-to-consumer advertising provides consumers with valuable information).

195. Rosenthal, *supra* note 193, at 504.

196. Family Smoking Prevention and Tobacco Control and Federal Retirement Reform, Pub. L. No. 111–31, § 2(12), 123 Stat. 1777 (2009).

197. Public Health Cigarette Smoking Act of 1969, 15 U.S.C. § 1336 (2006).

198. Capital Broad. Co. v. Mitchell, 333 F. Supp. 582, 583 (D.D.C. 1971).

199. *See* Capital Broad. Co. v. Kleindienst, 405 U.S. 1000 (1972).

advertising,[200] the FDA could, on its own, implement an approach more like the approach used for cigarettes by changing its regulation.

One way the FDA could accomplish an approach which differs between advertising aimed at consumers and advertising aimed at doctors would be to change the regulations defining what constitutes a label to be more consistent with the labeling as defined by Congress in the FDCA. If the regulations on labeling targeted only the types of labeling aimed at consumers—those that travel with the product as sold—then pamphlets and scientific information sent separately to doctors would be permissible.

This slight change in the regulations, which would allow manufacturers to communicate with doctors, would not affect broadcast media significantly, because the FDA would still have control over advertising.[201] Under the FDA's power to regulate drug advertising, the FDA can permissibly ban drug advertising on off label uses.[202] Moreover, governmental restrictions on broadcast media, even when the regulation is content-based, are viewed more leniently by courts under First Amendment precedent.[203]

As to the *Central Hudson* test, drug makers have most often had problems overcoming the fourth prong, which requires the regulation to be narrowly tailored.[204] Prohibiting manufacturers from broadcasting off-label uses on television only, or television and radio, is more narrowly tailored to the interests the FDA has asserted. Manufacturers would still have an incentive to seek new drug approval if they wanted to advertise drugs through these forms of mass advertising. Moreover, a ban only on direct-to-consumer advertising would better serve the FDA's goal of protecting people from the potential harms associated with drugs. While there certainly are risks associated with off-label use, those risks are not alleviated by the current speech restrictions, which prevent doctors from receiving information. In fact, risks associated with off-label use are significantly reduced when physicians prescribe in

200. It is questionable whether Congress could do this on its own. Congress has considered a law that would ensure that scientific information is not subject to FDA restrictions. But, at the same time, other members of Congress are actively seeking to limit the ability of drug manufacturers to advertise prescription drugs for approved uses. A further interesting question is whether this proposed law could have been a piece of health care reform.

201. *See* 21 U.S.C. § 352(n) (2006).

202. *Id.*

203. Red Lion Broad. Co. v F.C.C., 395 U.S. 367, 389–90, 400–01 (1969).

204. *See, e.g.*, Wash. Legal Found. v. Friedman, 13 F. Supp. 2d 51, 74 (D.D.C. 1998).

a manner that is consistent with scientific evidence. Allowing this communication would also promote safety, because it would facilitate the communication of safety information between manufacturers and physicians. Further, manufacturers would have an incentive to give warnings about off-label uses, because they could be subject to liability for failure to warn about these uses.

Moreover, this approach can resolve the current split on whether plaintiffs can recover in a failure to warn case resulting from an off-label use. Allowing manufacturers to promote off-label uses to doctors would make them liable for such uses. Allowing plaintiffs to recover from off-label uses might have an additional effect: the off-label use will be safer because of the advanced warnings. In other words, manufacturers who wish to promote an off-label use to doctors will have more incentive to provide thorough warnings if they know that the law will hold them liable.

Finally, allowing manufacturers to speak more freely about the scientific evidence concerning their products serves a number of policy goals. Scientifically validated claims increase knowledge within the medical profession, and manufacturers of products can play a role in this spread of knowledge by promoting new findings and making the information easily accessible. While medical knowledge is enhanced every day, the rate at which it advances can be overwhelming for practicing physicians. Moreover, the summary offered by manufacturers is helpful to familiarize physicians with new discoveries. One could argue that the information offered by these types of materials does not provide the level of information that a physician needs and that it could be skewed; however, because physicians are highly educated, the chance that they would rely solely on promotional materials is unlikely. Rather, the promotional materials would serve to enhance awareness.

While the government may have legitimate reasons to suppress manufacturer speech in the form of advertising to consumers through television or radio, the current restrictions on what a manufacturer can communicate to physicians is not necessary for any legitimate goal and suppresses information that could enhance patient safety.[205] Restrictions on manufacturer speech are particularly harmful because manufacturers are often the most knowledgeable about their products. Loosening the current restrictions would also allow manufacturers to solicit information about the off-label uses of their products from doctors, which could lead manufacturers to have even better knowledge about

205. *See* Dressler & Frader, *supra* note 25, at 476.

their own products.

## VII. CONCLUSION

The current ambiguities in the permissible speech regulations pertaining to off-label drug uses create problems and uncertainties. A better tailored approach is more likely to satisfy the constitutional protections of the First Amendment and result in better health care policy outcomes. An approach that bans advertising directed to consumers but not to physicians strikes the appropriate balance between the important public health goals, the favored use of generic drugs, and the established constitutional framework.

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